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Applicant: AKZO N.V.

PHARMACEUTICAL PREPARATION WITH ESTROGENIC EFFECT

The invention relates to a new pharmaceutical preparation having an estrogenic effect, which is suitable for being taken orally, and which contains a 17β-ester of estradiol, as well as to a method of making same and new 17β-esters of estradiol.

Estradiol and 17β-esters of this compound are known. In the medical practice, these estrogen compounds are used primarily for treating women having menopausal problems after removal of the ovaries, menstrual problems, and even after menopause, so as to avoid manifestations of deprivation. In such cases, the estrogens serve to compensate for a deficiency of endogenic estrogen (substitution therapy). Estrogens are further applied for treating certain kinds of inoperable carcinoma of the breast in women after menopause, and for treating carcinomas of the prostrate in men. The effect of estradiol-17β-esters is to be attributed to that of the estradiol, which is formed by hydrolysis of the ester in the body.

Estradiol is administered parenterally, primarily in the form of its 17β-esters. In this manner, a satisfactory effect is obtained with relatively small doses. Furthermore, the use of 17β-esters leads to a depot effect, so that an effective estrogen content in the plasma, which lasts for a few weeks, may be obtained by intramuscular injection. When using a mixture of 17β-esters at different absorption rates from the depot, and/or at different rates of hydrolysis in the plasma, an estrogen containing preparation may be obtained with a prolonged effectiveness, the effect starting very rapidly after the intramuscular administration and lasting, for example, a few weeks.

However, parenteral administration has also its disadvantages. The patients are not in a position to administer the injections themselves, and a physician or a medically trained person (nurse) is needed in the most cases. Furthermore, a repeated parenteral administration may lead to local reactions. The parenteral administration of long lasting preparations has moreover the disadvantage that its effect cannot be interrupted or terminated. Therefore, an oral intake would be clearly preferred over parenteral administration.

However, the foregoing effects of the parenteral administration cannot be achieved by the oral intake of estradiol or its 17β-esters, when the same quantities of the active substance are used. Instead, substantially larger quantities are necessary, sometimes up to 5 to 20 times as much.

The largest portion of the orally taken estradiol or estradiol-17β-ester is rapidly inactivated by the liver and separated as a metabolite. Only a portion of the administered dosis is available for the desired effect. It is also obvious that frequent intake in this manner will stress the liver and other organs, such as the kidneys to a greater extent, thereby causing possible undesired side effects.

It has been possible to increase clearly the effect of oral intake by introducing substituents into the estradiol molecules. Known examples therefor are: ethinyl estradiol (17α-ethinyl-$\Delta^{1,3,5(10)}$-estratriene-17β-ol); mestranol (3-methoxy-17α-ethinyl-$\Delta^{1,3,5(10)}$-estratriene-17β-ol); and quinestrenol (3-cyclopentyloxy-17α-ethinyl-$\Delta^{1,3,5(10)}$-estratriene-17-ol). The disadvantage of these "unnatural" estradiol derivatives is that their profile of action usually differs from that of the estradiol, which leads to the fact that, regardless of the advantage of a lesser dosage, it is necessary to take into account other effects, which are not always desired, in particular during a long lasting intake.

Surprisingly, it has now been found that the oral activity of estradiol can be improved substantially, when the estradiol is

taken in the form of its 17β-esters, which are derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms, and in the presence of a pharmaceutically tolerable, nonsteroidal lipoid. It has shown that the lower and higher, aliphatic carboxylic esters of estradiol have a much lesser effect, when they are taken under these circumstances in the same dosage.

Therefore, the invention relates to a new pharmaceutical preparation with estrogenic properties, which is suitable for oral intake and contains an ester of estradiol, and which is characterized in that it contains, in a pharmaceutical form for oral intake, one or more estradiol-17β-esters, which are derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms, together with a pharmaceutically suitable nonsteroidal lipoid. The invention also relates to the production of these preparations.

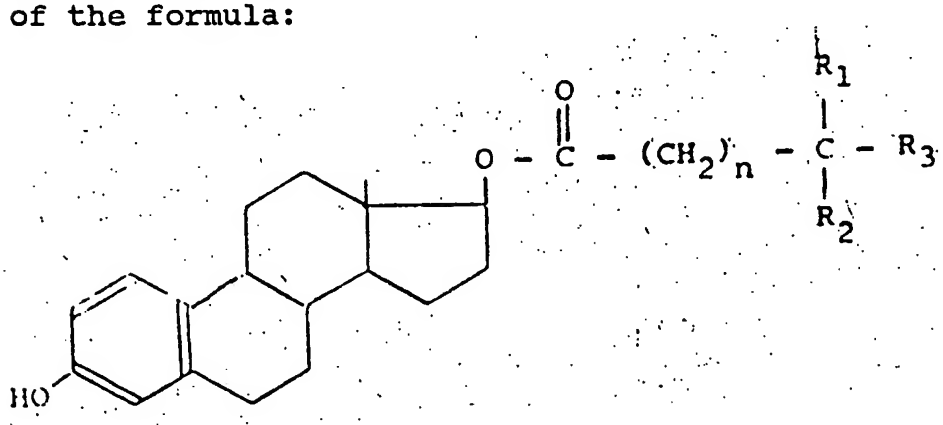
The term "aliphatic carboxylic acid" also comprises branched-chain, aliphatic and cycloaliphatic carboxylic acids.

The preparations of the present invention contain preferably one or more esters of estradiol, which are derived from an aliphatic carboxylic acid with 10 to 14 carbon atoms. It has shown that these esters possess the highest activity, in particular the α- and β-methyl-substituted, aliphatic carboxylic esters.

Examples for aliphatic carboxylic esters with 9 to 16 carbon atoms, from which the esters of estradiol are derived, include: pelargonic acid; capric acid; undecanonic acid; lauric acid; tridecanonic acid; myristic acid; pentadecanonic acid; decenoic acid; undecenoic acid; palmitic acid; and the branched-chain and cyclic analogues of these acids, such as α- (and β)-methylcaprylic acid; α- (and β-)-methylpelargonic acid; α- (and β-)-methylcapric acid; β,β-dimethylpelargonic acid; β-(p-methylcyclohexyl) propionic acid; β-(p-ethylcyclohexyl) propionic acid; β-(cyclohexyl) propionic acid; α- (and β-) methyl-β-cyclohexyl propionic acid; cyclo-dodecyl carboxylic acid; adamantane carboxylic acid; adamantyl acetic acid; and β-

(bicyclo-[2,2,2]-octyl) propionic acid. Preferably, the ester of estradiol is derived from capric acid; undecanonic acid; lauric acid; tridecanonic acid; myristic acid; or the α- or β-methyl substituted or cyclic isomers of these acids.

Numerous of the foregoing esters of estradiol are new compounds. Therefore, the invention further relates to the new esters of estradiol having the interesting, estrogenic properties of the formula:



wherein

n = 0, 1 or 2, normally 0 or 1, and preferably 0;

R_1 = an alkyl group with 1 to 10 carbon atoms, preferably a methyl group;

R_2 = H or an alkyl group with 1 to 10 carbon atoms, preferably one hydrogen atom;

R_3 = an aliphatic group with 1 to 18 carbon atoms, preferably 6 to 12 carbon atoms, which may contain one or more rings with 5 to 12 carbon atoms, preferably 5 to 7 carbon atoms; or R_1 and R_3 together with the carbon atom, to which they are linked, are a cycloaliphatic group with 7 to 12 carbon atoms; or R_1, R_2, and R_3 together with the carbon atom, to which they are linked, are a polycyclo-aliphatic group with 6 to 12 carbon atoms, preferably 8 to 10 carbon atoms. The cycloaliphatic or polycyclo-aliphatic group may be replaced with an aliphatic group with 1 to 6 carbon atoms, on the condition that the total number

of carbon atoms in the ester groups is in the range from 8 to 20, preferably from 9 to 16, and in particular from 10 to 14.

Pharmaceutically suitable, nonsteroidal lipoids are understood to be vegetable and animal oils and fats, consisting of mono-, di-, or triglycerides of different fatty acids, or substances containing same as their main ingredient, fatty acid esters of alcohols, higher aliphatic alcohols, saturated or unsaturated fatty acid, commercially available synthetic or half-synthetic mono-, di-, and triglyceride oils and glycerol ether, certain waxes and mixtures of two or more of the foregoing substances. The lipoidal substance is liquid, preferably at room temperature, i.e., at a temperature from about 10 to about 30°C. The ester of estradiol is dissolved in the lipoidal substance, and subsequently the solution may be processed to a preparation or, as the case may, to a pharmaceutical form of administration. At room temperature, a portion of the ester may be suspended in the liquid lipoid, the quantities of the esters and lipoidal substance being adapted to one another, so that at the body temperature the ester is totally dissolved in the lipoidal substance. The intensification of the oral effectiveness of the ester of estradiol in accordance with the invention appears to be greatest, when a lipoidal substance is used that is liquid at room temperature.

Examples for lipoidal substances, which may be used for the preparations of the present invention include peanut oil; castor oil; linseed oil; soybean oil; sunflower seed oil; olive oil; liver oil (fish liver oil); ethyl oleate; oleyloleate; glyceryl trioleate; glyceryl dioleate; glycerylmonooleate; cetyl alcohol; stearyl alcohol;, capric acid;, undecenoic acid; undecanonic acid; lauric acid; oleic acid; synthetic glycerides of saturated fatty acids with 8 to 10 or 12 carbon atoms, such as the commercially available product Sydermin GTG and Miglyol 812; polyoxyethylene derivatives of glycerol, such as the commercially available product Labrafil 1944, bee wax; and mixtures of two or more of these substances.

The invention relates to an oral, pharmaceutical preparation with estrogenic effectiveness. It is also possible to produce an orally effective pharmaceutical preparation, which has besides its estrogenic properties, also androgenic or gestagenic properties, in that an orally effective androgen or gestagen is added to the preparation.

Orally effective, pharmaceutical preparations, which have both an estrogenic and an androgenic effectiveness, are known. Such preparations contain normally an orally effective estrogen, such as 17α-ethinyl-estradiol or -mestranol, as the estrogenic component, and an orally effective androgen, such as 17α-methyl-testosterone as the androgenic component. The two components are present at a certain ratio. Conditions, under which such preparations are used, include menopausal problems, improvement of sleep and general state of health of older women, in cases of frigidity, hypogonadism, vascular disorders, osteoporosis, and after a total hysterectomy. Such preparations have a positive influence on the protein and calcium metabolism, and can reduce or normalize a disorder of the hormonal balance during menopause or after total hysterectomy. If these preparations are used in cases of frigidity, the androgenic component will increase the libido, and the estrogenic component will contribute to a restoration of a possible atrophic mucous membrane. In the case of osteoporosis, the estrogenic component leads to a reduction of the osteoclastic activity, and the androgenic component stimulates the formation of the bone matrix.

A preferred, orally effective androgen for incorporation in the estrogenic preparation of the present invention is the use of one or more esters of testosterone and/or 5α-dihydrotestosterone ester, which are derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms, preferably 10 to 12 carbon atoms.

The androgenic ester may be derived from the same aliphatic carboxylic acid, such as the ester of estradiol and, preferably, it is derived from capric acid, undecanonic acid, or lauric acid.

The presence of the oily component in the preparation of the present invention leads like to an enhancement of the oral, androgenic effectiveness of the ester of testosterone and/or 5α-dihydrotestosterone ester. In this manner, a preparation is obtained for oral administration, which possesses both an estrogenic and an androgenic activity, which has moreover the advantage that the effect is based on the effect of natural hormones, which are formed in the body by hydrolysis of the esters.

Likewise known are pharmaceutical preparations with an estrogenic and a gestagenic activity. This combination is known primarily from orally effective contraceptives of the so-called combination type, in which an orally effective substance, such as chlormadinone acetate, lynestrenol, noresthisterone, norethynodrel, or norgestrel, is combined with an orally effective estrogenic substance, such as ethinyl estradiol or mestranol. In such preparations, the estrogenic component may be replaced with one or more esters of estradiol, which are derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms together with a lipoidal substance of the present invention. With respect to the combination of an estrogen with a gestagen within the scope of the present invention, attention is directed primarily to combination preparations, which are used during and after menopause, after a total hysterectomy, and in the case of hypogonadism, and in which attempts are made to restore the hormonal balance so far as to suppress, besides other positive effects on bodily functions, in particular osteoporosis (see J.C. Gallagher and B.E.C. Nordin, "The Hormone," Vol. XXXVII, pp. 59-73 (1973), under the subheading: "Hormones and Calcium Metabolism"). For making such preparations, which may be used for such an indication, it is advantageous to incorporate likewise an orally effective, gestagenic substance in the preparation of the present invention, for example, noresthisterone, lynestrenol, or ethynodiol diacetate.

The preparation of the present invention may be taken orally in various forms of dosage, for example, in the form of tablets, capsules, grains, pills, boli, dragées, powders, granules, or microcapsules. Besides the estrogenic ester or esters, the lipoidal substance, and, if need be, the androgenic or gestagenic combination, the form of dosis may contain one or more of the standard excipients, benzyl alcohol for increasing the solubility of the active ingredient in the oil component, water, thickeners, such a gelatin or agar, polyethylene glycols, lactose, starch, talcum, or magnesium stearate. Other substances, such as preservatives, emulsifiers, stabilizers, humectants, flavors, colorants, fillers, binders, and/or capsule materials may likewise be used, if need be.

The capsules may be gelatin capsules with a soft or a hard shell, in which the active ingredient and the lipoid may be present in the form of granules or finely distributed in the mixture, or in the form of an oily solution or suspension.

The combination of the estradiol-17β-ester and the lipoid, when liquid or semiliquid, may also be processed to solid, oral forms of administration, such as pills or tablets. To this end, the oily suspension of the estradiol-17-ester is absorbed, for example, in calcium phosphate, lactose, or cellulose derivatives, and then processed in the usual manner to tablets or pills. Combinations of estradiol-17β-ester with lipoids, such as glyceryl monooleate or capric acid, which are solid or halfsolid at room temperature, but liquid at body temperature, may be granulated and processed to dragées or tablets.

As aforesaid, the esters of estradiol in accordance with the invention are administered, preferably dissolved in lipoidal substances, which are liquid at room temperature, such as, for example, vegetable and animal oils, oleic acid, linolenic acid, or undecanonic acid. If an androgenic or gestagenic component is present, same will be dissolved likewise in the oil besides the ester of estradiol.

The most favorable oral form of administration for this liquid form of the preparation in accordance with the invention are gelatin capsules or microcapsules. By a standard process, the oily solution, which contains the active ingredients and, possibly, other substances, is enclosed in soft gelatin capsules or microcapsules of the desired size, which contain the desired quantity of the active ingredients. The microcapsules may also be processed to tablets or pills by standard pharmaceutical or pharmacological processes.

The concentration of estradiol-17β-ester or esters in the preparations of the present invention may vary within wide ranges, the quantity by weight of estradiol-17β-ester or esters not exceeding the quantity by weight of the lipoidal substance or, in other words, the concentration of estradiol-17β-ester or esters in the preparation amounts to 50% by weight or less, and is generally in a range from 0.01 to 10% by weight.

As aforesaid, the quantity by weight of the lipoidal substance in the preparation of the present invention is equal to, or higher than, the quantity by weight of the estradiol-17β-ester. Depending on the other ingredients contained in the preparations (excipients, shell of capsule, coating) the quantity of the lipoidal substance varies from 5 to 95% by weight, ranges normally from 25 to 80% by weight. The quantity of estradiol-17β-ester per unit of dosis, for example, capsule or tablet, may vary likewise within wide ranges, and is, for example, from 0.001 to 2 mg, preferably 0.005 to 1 mg.

If the androgenic ester is present in the preparation of the present invention, its quantity per dosis unit will range from 0.5 to 400 mg. The condition that the quantity by weight of the androgenic ester be no greater than the quantity by weight of the lipoidal substance, will apply likewise in this instance. If the gestagenic substance is contained in the preparation of the present invention, its quantity per dosis unit ranges from 0.1 to 20 mg and preferably from 0.2 to 10 mg.

It was possible to demonstrate on castrated female rats the extremely good estrogenic properties of the preparations in accordance with the invention with the aid of the known Allen-Doisy test (J.A.M.A. (1923), 81, pp. 819-821). The estradiol-17β-esters were administered dissolved in peanut oil. The results are shown in Table A.

TABLE A

Estradiol-17β-ester	Dosis		
	8 μg	16μg	32 μg
-formate	0/8	0/8	1/8
-pentanoate	0/8	0/8	0/8
-octanoate	0/8	1/8	2/8
-decanoate	2/8	6/8	7/8
-α-methyl decanoate	8/8	8/8	8/8
-β-methyl decanoate	6/8	8/8	8/8
-undecanoate	2/8	7/8	8/8
-dodecanoate	2/8	6/8	7/8
-tetradecanoate	1/8	6/8	6/8
-hexadecanoate	0/8	0/8	6/8
-octadecanoate	0/8	0/8	2/8

Tests with other, lipoidal substances, such as sesame oil, soybean oil, glyceryl trioleate, oleic acid, and undecenoic acid, led to similar results. It is obvious that the estradiol-17β-esters, which are derived from carboxylic acids with 9 to 16 carbon atoms, are substantially more effective than the other esters, and that in particular the esters with 10 to 14 carbon atoms in the ester group are very active.

Clinical tests with women, whose ovaries had been removed, and women in menopause, who all took by mouth a daily dosis of 0.1 to 0.5 mg estradiol-17β-ester in the form of a preparation in accordance with the invention, showed a very favorable estrogenic effect, which suggests the effectiveness of the preparation in the EDS therapy.

In clinical tests with women after the menopause, who took for six weeks a daily dosis of 1 to 3 dosis units of an estrogen and an estrogen-gestagen preparation in accordance with the invention, a clear decrease in the plasma calcium content was observed, which suggests an anti-osteoporotic effect.

The invention is described in more detail with reference to the following examples.

EXAMPLE 1

Soft Gelatin Capsules

A sterile solution of estradiol-17β-decanoate in peanut oil, containing 4.167 g per liter, was prepared. This solution was filled in soft-shelled gelatin capsules, while carefully observing aseptic conditions. The obtained soft gelatine capsules contained 0.12 ml, so that the quantity of the effective ingredient was 0.5 mg in each capsule. The capsule wall consisted of 70% gelatine, 16% glycerol, 12% sorbitol, 0.5% of the sodium salts of ethyl/propyl-p-hydroxybenzoate, 0.5% TiO_2, and 1.1% cochineal red (colorant).

In similar manner, a number of estradiol-17β-esters was processed in different lipoidal substances to soft-shelled gelatine capsules according to the following table:

TABLE B

-17β-ester	Lipoidal Substance	Contents of Capsule	Active Ingred. per Capsule (mg)
-decanoate	Oleic acid	0.12	0.25
α-methyl decanoate	Sesame oil	0.08	0.1
β-methyl decanoate	Undecenoic acid	0.18	0.2
-undecanoate	Soybean oil	0.12	0.2
-dodecanoate	Ethyloleate	0.12	0.25
-tetradecanoate	Linseed oil	0.18	0.5
α-methyl-β-cyclohexyl-propionate	Peanut oil	0.18	0.5
Cyclododecanyl-carboxylate	Oleic acid	0.12	0.5

EXAMPLE 2

Tablets

Estradiol-17β-decanoate	0.5 mg
Capric acid	20.0 mg
Lactose	145.0 mg
Potato starch	82.5 mg
Magnesium stearate	1.5 mg
Citric acid	0.5 mg
	250.0 mg

The estradiol-17β-undecanoate [sic] was dissolved in capric acid, while being slightly heated. Subsequently, the solution was homogeneously absorbed in lactose. After mixing with potato starch, citric acid, and some water, the thus-obtained granular substance was dried. The dried granular substance was mixed with the magnesium stearate and pressed to tablets in the usual manner.

In similar manner, tablets of the following composition were prepared:

Estradiol-17β-undecanoate	0.5 mg
Testosterone-undecanoate	40.0 mg
Glycerylmonooleate	100.0 mg
Lactose	308.0 mg
Potato starch	150.0 mg
Magnesium stearate	1.5 mg
	600.0 mg
Estradiol-17β-α'-methyl decanoate	0.5 mg
Lynestrenol	2.5 mg
Bee wax/stearyl alcohol	10.0 mg
Lactose	118.0 mg
Potato starch	68.0 mg
Magnesium stearate	1.0 mg
	200.0 mg

EXAMPLE 3

Hard-Shelled Gelatin Capsules

Estradiol-17β-dodecanoate	0.25 mg

Chlormadinone acetate	4.00 mg
Lauric acid	95.75 mg
	100.00 mg

Estradiol-17β-dodecanoate and chlormadinone acetate were dissolved in lauric acid at 50°C. After cooling, the solid mixture was pulverized, and hard-shelled gelatine capsules were filled with the fine-sized mixture (100 mg of the mixture per capsule).

EXAMPLE 4

Soft Gelatin Capsules

Soft gelatine capsules with the following contents were prepared in accordance with Example 1.

a)	Estradiol-17β-decanoate	0.02 mg
	Testosterone-17β-decanoate	10.00 mg
	Oleic acid	0.18 ml
b)	Estradiol-17β-undecanoate	0.1 mg
	Norethisterone	2.0 mg
	Peanut oil	0.12 ml

EXAMPLE 5

Preparation of the New Esters

To a solution of 2 g estradiol in a mixture of 8 ml pyridine in 8 ml acetone, which was cooled to -10°C, a solution of 4 ml α-methyl-β-cyclohexyl-propionylchloride in 12 ml acetone was added dropwise. The mixture was stirred 16 hours at 0°C, and 6 hours at room temperature. After cooling to -10°C, a solution of 1 ml α-methyl-β-cyclohexyl-propionylchloride in 5 ml acetone was added, and the mixture was stirred 16 hours at room temperature. The reaction mixture was poured into ice water (8 g) and stirred for some time, so as to destroy excessive acid chloride. The mixture was extracted with methylene chloride. The extraction (4 g) containing estradiol-3,17β-diester was evaporated to dryness, and the residue was dissolved in a mixture of methanol (19 ml) and tetrahydrofuran (19 ml). The solution was cooled, and subsequently a solution of 350 mg calcium hydroxide in a mixture of 4.8 ml methanol and 2 ml tetrahydrofuran was added. The

mixture was stirred 4 hours, during which the temperature rose gradually to 0°C. The reaction mixture was poured into ice water. As a result of extracting with a methylene chloride, chromatographing via a silica gel with the aid of toluol/ethylacetate 95:5, and recrystallizing from ether, 1.5 g estradiol-17β-(α-methyl-β-cyclohexyl propionate), FP 154-156°C was obtained; $[\alpha]^{20}_D$ = + 39°(in CH_2Cl_2).

In similar manner, the following 17β-esters of estradiol were prepared:

α-methyl decanoate
β-methyl decanoate
β,β-dimethyl decanoate
β-cyclohexyl butyrate
Cyclododecyl carboxylate
β-propyl hexanoate
τ,τ-diethyl hexanoate
Adamantane-1'-carboxylate
α,α-dimethyl-octadecanoate
α-ethyl heptanoate
Cycloheptyl carboxylate
Cyclooctyl acetate
α,α-dimethyl heptanoate
α-methyl hexadecanoate
α-ethyl tetradecanoate
β-ethyl hexanoate
β-butyl heptanoate
β,β-dimethyl nonanoate

C L A I M S

1. Pharmaceutical preparation with estrogenic effectiveness for oral administration, containing at least one 17β-ester of estradiol, the ester group of which is derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms, and a

pharmaceutically suitable carrier comprising a nonsteroidal lipoid.

2. Preparation as in claim 1, characterized in that the ester is derived from an aliphatic carboxylic acid with 10 to 14 carbon atoms.

3. Preparation as in claim 1 or 2, characterized in that the lipoid is liquid at room temperature.

4. Preparation as in claims 1-3, characterized in that it contains in addition an orally effective androgen or gestagen.

5. Preparation as in claim 4, characterized in that the orally effective androgen is an ester of testosterone and/or 5α-dihydrotestosterone, the ester group of which is derived from an aliphatic carboxylic acid with 9 to 16 carbon atoms.

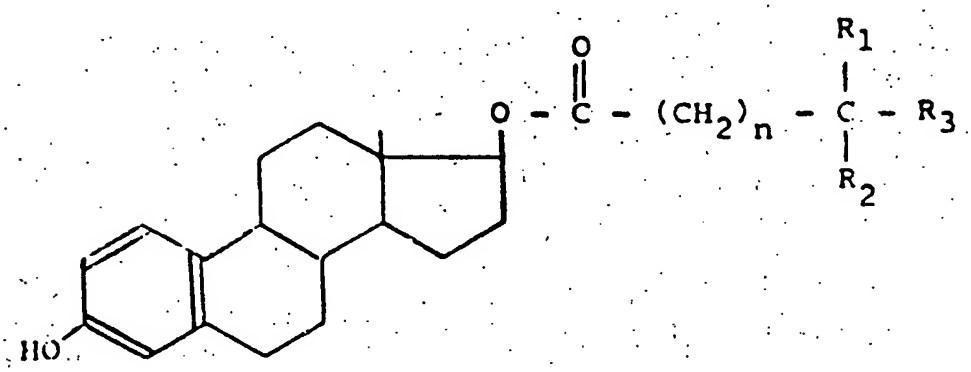
6. Preparation as in claims 1-5, characterized in that the ester of estradiol amounts to 50% by weight or less, preferably 0.01 to 10 % by weight of the preparation.

7. Preparation as in claim 6, characterized in that the lipoid is present in a quantity equal to, or larger than, the ester of estradiol.

8. Preparation as in claim 7, characterized in that the lipoid amounts to 5 to 95% by weight of the preparation, preferably 25 to 80% by weight.

9. Preparation as in claims 6-8 in the form of unit doses, comprising 0.001 to 2 mg ester of estradiol, preferably 0.005 to 1 mg.

10. 17β-ester of estradiol for making the preparations of claims 1-10, characterized by the formula:



wherein

n = 0.1 or 2, normally 0 or 1, preferably 0;

R_1 = an alkyl group with 1 to 10 carbon atoms, preferably CH_3;

R_2 = H or an alkyl group with 1 to 10 carbon atoms, preferably H;

R_3 = an aliphatic group with 1 to 18 carbon atoms, preferably 6 to 12 carbon atoms, which may contain one or more rings with 5 to 12 carbon atoms, preferably 5 to 7 carbon atoms; or R_1 and R_3 together with the carbon atom, to which they are linked, are a cycloaliphatic group with 7 to 12 carbon atoms; or R_1, R_2, and R_3 together with the carbon atom, to which they are linked, are a polycycloaliphatic group with 6 to 12, preferably 8 to 10 carbon atoms, the cycloaliphatic or polycycloaliphatic group being replaced, if need be, with an aliphatic group with 1 to 6 carbon atoms, and the total number of carbon atoms in the ester group ranging from 8 to 20, preferably 9 to 16, and in particular 10 to 14.